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Safety and efficacy of belimumab plus standard therapy for up to 13 years in patients with systemic lupus erythematosus

Running title: Long-term belimumab therapy for systemic lupus erythematosus

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ROLE OF THE STUDY SPONSOR

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CONFLICTS OF INTEREST

- DJW: Research grants, clinical studies (all <$10,000): GSK; consulting fees (all <$10,000): GSK, Lilly, EMD Serono, and Celgene

- EMG: Research grants: GSK, Aurinia, Genentech
- JTM: Grant/research support from Xencor, BMS and GSK; consultant for GSK, EMD Serono, Lilly, AstraZeneca, BMS, Janssen, Amgen, Sanofi, AbbVie, Immupharma, Servier, InCyte, ILTOO, Glenmark, Astellas (all <$10,000), Celgene, and Remegen (both >$10,000)
- RAF: Research grants, clinical studies: GSK
- WS: Clinical studies: GSK, Pfizer; consulting fees (<$10,000): Johnson & Johnson
- WWC: Research grants, local principal investigator, consulting fees (<$10,000): GSK
- AW: nothing to disclose
- JDM: Clinical studies: GSK, MedImmune, Anthera, Johnson & Johnson, Lilly, Xencor, Astra Zeneca, Eli Lilly, and Gilead
- WJM: Clinical studies: Eli Lilly, GSK
- MP: Consulting fees (<$10,000): GSK; Research support (institutional, >$10,000): GSK
- DAR and BJ: Employees of GSK and hold shares in the company
- JF: Employee and held shares in GSK at the time of the study
- AH: Employee of GSK at the time of the study and holds shares in the company

DATA AVAILABILITY

Anonymized individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com

ABSTRACT

Objective

Investigate long-term safety and efficacy of intravenous (IV) belimumab plus standard systemic lupus erythematosus (SLE) therapy (SoC) in active, autoantibody-positive SLE.

Methods

This was a multicenter, open-label, continuation study of IV belimumab given every four weeks with SoC in patients with SLE who completed a Phase II, double-blind study. Adverse events (AEs) and laboratory data were monitored from the first belimumab dose (in either study) until 24 weeks after the final dose. Efficacy assessments (every 16 weeks) included SLE Responder Index (SRI), flares and corticosteroid use (every 4 weeks).

Results

Of 476 patients in the parent study, 298 (62.6%) entered the continuation study; 96 (32.2%) remained in the study. Patients received belimumab for up to 13 years (median [range] 3334.0 [260, 4332] days; total belimumab exposure 2294 patient-years; median [range] number of infusions 115.5 [7, 155]). The percentage of patients with AEs each year remained stable or decreased. The majority of patients maintained normal IgG levels and the rate of infections remained stable. The percentage of patients who achieved an SRI response increased from 32.8% (Year 1) to 75.6% of those remaining on treatment at Year 12. Corticosteroid dose decreased for patients receiving >7.5 mg/day at baseline.

Conclusions

This study reports the longest duration of belimumab treatment in clinical trials. Belimumab was well tolerated with no new safety concerns, and efficacy was maintained in patients who continued the study. For patients who initially respond to belimumab, the treatment continues to be well tolerated and provides long-term disease control.

KEY WORDS

Belimumab, long-term treatment, systemic lupus erythematosus

Intravenous (IV) belimumab (10 mg/kg) is approved for the treatment of active, autoantibody-positive systemic lupus erythematosus (SLE) in over 60 countries including the US, Japan, and those in Europe.[1-3] A Phase II, placebo-controlled, dose-ranging trial (LBSL02; NCT00071487) of IV belimumab plus standard therapy (SoC) in 449 patients with active, autoantibody-positive SLE demonstrated that belimumab was well tolerated through 52 weeks.[4] This study also informed the design of Phase III trials,[5, 6] and the development of the SLE Responder Index (SRI).[7] Two pivotal Phase III trials further demonstrated the efficacy and safety of belimumab IV plus SoC for up to 76 weeks.[5, 6] To investigate the long-term safety and efficacy of belimumab plus SoC, a continuation study of LBSL02 was conducted. Previous interim analyses from this study have shown that belimumab was well tolerated, and disease control was maintained through 7 years.[8, 9] Here we report the final analysis of this study, which is currently the longest SLE therapy study measuring efficacy and safety [9] and includes patients who received belimumab for up to 13 years.

MATERIALS AND METHODS

Study design

This was a multicenter, open label, continuation study (GlaxoSmithKline Study BEL112626/NCT00583362) of belimumab IV plus SoC in patients with SLE who achieved a satisfactory response in a Phase II, double-blind study (**Supplementary Figure 1**).[4] Patients who completed the double-blind phase could continue in the open label, 24-week extension study. In the extension, patients who had received placebo switched to 10 mg/kg IV belimumab, and those previously receiving belimumab either continued at the same dose (1, 4, or 10 mg/kg) or switched to 10 mg/kg, based on their response at the end of the double-blind phase. Patients who completed the extension study, who had an improvement in Physician's Global Assessment (PGA) score compared with baseline (prior to the first dose of belimumab) and had no severe flare (defined by the Safety of Estrogens in Lupus Erythematosus-National Assessment-SLE

Disease Activity Index [SELENA-SLEDAI] Flare Index [SFI][10]) in the last 30 days of the extension study, were eligible to enter the continuation study. The protocol for the continuation study has been reported previously.[8, 9] Briefly, all patients received 10 mg/kg IV belimumab every 4 weeks until they withdrew from the study or the criteria for ending the study were met (whichever came first, 10 years from the enrolment of the last patient or ≤100 patients participating in the study). To prevent unnecessary long-term exposure to belimumab for patients who did not benefit from treatment, stopping rules were applied (**Supplementary Table 1**). Following withdrawal from the study, patients were monitored for an additional 24 weeks.

Institutional review board or ethics committee approval was obtained for all study sites. All patients gave informed consent before entering the long-term study.[8, 9]

Assessments

Safety was monitored from the first dose of study treatment until 24 weeks after the final dose, with adverse events (AEs) and laboratory data recorded. Clinical laboratory tests included hematology, chemistry, routine urinalysis, immunoglobulins (IgG, IgA, IgE, IgM), and anti-drug antibody testing and were performed every 8 weeks.

Efficacy assessments were made at 16-week intervals unless otherwise stated and included SRI4 response [7], SELENA-SLEDAI [10], British Isles Lupus Assessment Group (BILAG) [11], PGA (8 week intervals), SFI, change in corticosteroid use (4-week intervals) and serologies (including complement C3/C4, and autoantibodies). Corticosteroid doses are reported as prednisone equivalent doses. Low disease activity was defined as SELENA-SLEDAI ≤2 and a prednisone dose of ≤5 mg/day.

Data analyses

All analyses were conducted for the modified intent-to-treat population, defined as all patients who received at least one dose of belimumab in the continuation study. No formal statistical hypothesis testing was performed, and all analyses

were exploratory. All analyses were performed using descriptive statistics. Post hoc analyses included AE rates (per 100 patient-years) by preferred term, last observation carried forward (LOCF) for SRI response rate among patients who withdrew, categorical analyses of SELENA-SLEDAI and PGA, the cumulative time patients' prednisone dose was ≤7.5 mg/day, the number of patients with low disease activity at each study visit and normalization of anti-double-stranded deoxyribonucleic acid (dsDNA) antibodies, C3, and C4.

Baseline data were recorded prior to the first dose of belimumab (in either the parent study or extension study for those who previously received placebo).

Data analyses were performed using SAS software, version 9.4.

RESULTS

Study population and patient disposition

Four hundred and seventy-six patients were randomized in the parent study to receive belimumab IV or placebo, added to SoC. Of these, 298 (62.6%) entered the continuation study; 96 (32.2%) remained in the study at study end (**Figure 1A**), and 88 (29.7%) remained in the study for ≥11 years. Total belimumab exposure was 2294 patient-years. The median (range) duration of exposure was 3334.0 (260, 4332) days, and the median (range) number of infusions was 115.5 (7, 155). Patient self-withdrawal was the most common form of withdrawal (**Figure 1**); the most frequent reasons for this were a desire to become pregnant and difficulties attending the clinic due to location, travel or time constraints. Withdrawal due to lack of efficacy seldom occurred throughout the study and reached a maximum of six patients in Year 3. At Years 5, 7, and 10, the percentages of patients remaining in the study were 70.1%, 60.1%, and 44.3%, respectively.

Baseline demographics and disease characteristics have been reported previously.[8, 9] The majority of patients were female (93.2%), and the mean ± standard deviation (SD) age was 43.0 ±11.58 years (**Table 1)**. At baseline, the mean ± SD duration of SLE was 9.1 ± 7.80 years; mean ± SD SELENA-SLEDAI

was 8.4 ± 4.68; 31.1% of patients were receiving >7.5 mg/day prednisone, and 35.5% were not receiving corticosteroids; 81.3% of patients were antinuclear antibody-positive.

Safety: adverse events

The percentage of patients reporting AEs each year remained stable or decreased throughout the study (**Table 2, Supplementary Table 2**). The most frequent AEs (≥15.0/100 patient-years) were arthralgia (29.3/100 patient-years), upper respiratory tract infection (29.0/100 patient-years), sinusitis (16.9/100 patient-years), urinary tract infection (16.2/100 patient-years), and headache (15.0/100 patient-years). The rates of the most frequent AEs were stable or declined overall from Year 1 to Year 11+ (**Supplementary Table 3**). The most common serious AEs (≥0.5 events/100 patient-years) were pneumonia (0.9/100 patient-years), osteoarthritis (serious because of the need for hospitalization for elective surgical management; 0.8/100 patient-years), non-cardiac chest pain (0.7/100 patient-years), pyrexia (0.6/100 patient-years), cellulitis, chronic obstructive pulmonary disease, abdominal pain, viral gastroenteritis, and vomiting (all 0.5/100 patient-years). Forty-four patients (14.9%) discontinued belimumab or withdrew from the study because of an AE. AEs that resulted in discontinuation or withdrawal of more than one patient were invasive ductal breast carcinoma (n=3, 1.0%) and hypogammaglobulinemia (n=2, 0.7%).

The rate of serious infections and infestations remained steady from Year 1 (3.7/100 patient-years) through Year 11 (6.7/100 patient-years; **Table 2**). The rate of infections of special interest was also stable throughout the study (5.1/100 patient-years; **Table 2**). The rate of malignant neoplasms excluding non-melanoma skin cancer was 0.6/100 patient-years; there were no events in Years 1, 2, 8, 11, and 11+; the rate was highest in Year 10 (2.1/100 patient-years). There were no cases of progressive multifocal leukoencephalopathy (PML) in this study.

The rate of depression was 9.8/100 patient-years (237 events). Six events of suicide/self-injury occurred (0.2/100 patient-years), four of which were serious, with one resulting in death. There were seven deaths in the study, and one during the follow-up period. Causes of death were pneumonia (n=2; one was due to an opportunistic infection), cardiac arrest, coronary artery disease, acute respiratory distress syndrome, respiratory failure, retroperitoneal hemorrhage, and suicide.

Safety: clinical and laboratory parameters

Of hematology parameters investigated (activated partial thromboplastin time, hemoglobin, neutrophil count, platelets, and prothrombin time), the only one for which ≥10% of patients had a Grade 3 (severe) or Grade 4 (potentially life-threatening) value was low neutrophil count (Grade 3: 15.2% [45/296]; Grade 4: 2.7% [8/296]) (**Supplementary Table 4**). Gamma-glutamyl transferase was the only chemistry measurement in which >5% of patients experienced a Grade 3 or 4 value (Grade 3: 5.7% [17/296]; Grade 4: 3.0% [9/296]) (**Supplementary Table 4**). With the exception of protein excretion rate (18/296, 6.1%), fewer than 5% of patients had Grade 3 or 4 abnormalities for urinalysis components (data not shown).

The percentage of patients with IgG, IgM and IgA levels below the lower limit of normal (LLN) increased during the study (**Figure 2A**). There were 16.2% (48/296), 57.4% (170/296), and 13.5% (40/296) of patients who had IgG, IgM and IgA levels below the LLN, respectively, at more than one visit. No IgE levels were below the LLN. The majority (65.9% [195/296]) of patients had normal IgG levels throughout the study; 4.1% (12 patients) had Grade 3 IgG values (250–399 mg/dL), and 2.4% (7 patients) had Grade 4 IgG values (<250 mg/dL) (**Supplementary Table 4**). Of 19 patients who had Grade 3 or 4 IgG values, 17 (5.7%) had at least a two-grade shift from baseline.

Although there was a reduction in IgG during the study, the rate of infections (serious and non-serious) remained stable over time (**Table 2**). A post hoc analysis showed that 4/19 patients with Grade 3 or 4 IgG abnormalities had a

severe and/or serious infection (viral gastroenteritis, urinary tract infection and sepsis, bronchitis, cellulitis) ≤28 days before their Grade 3 or 4 IgG reduction.

Efficacy

As the number of participants declined, the percentage of patients who achieved an SRI response increased from 32.8% (88/268) at Year 1 Week 16 to 75.6% (68/90) at Year 12 Week 32 (**Figure 3A**). Among patients who withdrew from the study and had a SELENA-SLEDAI score of ≥4 at baseline, 59.8% (110/184) were SRI responders (LOCF) at the time of withdrawal. The percentage of patients with a ≥4-point reduction from baseline in SELENA-SLEDAI also increased from 33.7% (99/294) at Year 1 Week 16 to 76.7% (69/90) at Year 12 Week 32. The percentage achieving a SELENA-SLEDAI score ≤2 increased throughout the study from 8.4% (25/296) at baseline to 62.2% (46/74) at Year 12 Week 48 (**Figure 3B**). The percentage with no new BILAG A organ domain score and no more than 1 new BILAG B organ domain score compared with baseline increased over time, ranging from 65.9% (195/296) during Year 1 to 94.3% (83/88) at study end (**Figure 3C**). The percentage with low PGA scores (0–1) increased during the study, and at all time points few patients had PGA scores >2.5 (**Figure 3D**).

Rates of SFI flares and severe SFI flares were 1.1 and 0.1/patient-year, respectively. The occurrence of flares was highest in Year 1 and was consistently low throughout the study (**Figure 4A**).

At baseline, 190 patients (64.5%) were receiving corticosteroids; of these, 25 (13.2%) discontinued corticosteroids for the remainder of the study. The median (range) percentage change from baseline in daily prednisone dose was greatest at Year 13 Week 24 (88.00% [−100 to 33.33]; n=16) (**Figure 4B**). Of patients receiving >7.5 mg/day prednisone at baseline, the percentage achieving ≤7.5 mg/day increased over time (**Figure 4C**) to a maximum of 53.8% (14/26) at Year 12 Week 48. Of the 99/296 patients receiving ≤7.5 mg/day prednisone at baseline, 23 (23.2%) maintained a dose of ≤7.5 mg/day throughout the study. The percentage of patients who had an increase in prednisone dose to

>7.5 mg/day increased from Year 1 Week 8 (3.0% [6/200]) to a maximum of 20.4% (11/54) at Year 12 Week 40 (**Figure 4C, Supplementary Figure 2**).

The percentage of patients achieving low disease activity (SELENA-SLEDAI ≤2 and prednisone dose ≤5 mg/day) increased throughout the study from 13.9% (41/294) at Year 1 Week 16 to a maximum of 57.1% (4/7) at Year 13 Week 32 (**Figure 4D**).

Disease activity following withdrawal from the study

Following withdrawal from the study, there was little change in disease activity at follow-up Weeks 8 and 24 (**Supplementary Table 5**). The percentage of patients who achieved an SRI response increased slightly from follow-up Week 8 (61.9%, 122/197) to follow-up Week 24 (64.0%, 114/178). However, the percentage of patients with SFI flare (Week 8: 20.5%, 45/219; Week 24: 21.1%, 42/199) or severe SFI remained stable (Week 8: 2.7%, 6/219; Week 24: 3.0%, 6/199).

Biomarkers

Anti-dsDNA autoantibody levels decreased in patients who were positive at baseline (**Figure 2B**), and of 152 patients with levels above the upper limit of normal at baseline, 23 (15.1%) returned to normal and remained normal during the study. Complement levels increased in patients who had low levels at baseline (**Figure 2C, 2D**); and of 88 patients with low C3 and 116 patients with low C4 at baseline, the levels in 7 (8.0%) and 14 (12.1%) patients, respectively, normalized and remained normal during the study.

DISCUSSION

This study provides up to 13 years of data on the safety and efficacy of belimumab plus SoC for the treatment of SLE. That approximately one-third of patients continued to receive belimumab for at least 10 years is extraordinary, particularly in light of adherence rates to other medications used for and studied in SLE [12]. Few patients withdrew due to a lack of efficacy, and the long-term safety profile of belimumab was acceptable.

The rates and nature of AEs were consistent with the known safety profile of belimumab,[4-6, 8, 9, 13, 14] and there was no increase in AEs over time. The rate of self-injury/suicide remained low throughout this study and was similar to that reported for the open-label extension of the Phase III studies, which investigated the safety of belimumab for up to 6 years in nearly 1000 patients.[13] The incidence of death was 2.7% (0.3/100 patient-years); this compares with 1.1% reported until Year 6 for the continuation study of the Phase III studies.[13] Other SLE studies have reported higher rates of mortality than this study; for example, a multinational study of 9547 patients with an average follow-up of 8.1 years reported a 13.1% incidence of death;[15] and a study in the US estimated a 10-year mortality rate of 26% in patients with SLE versus 19% in matched controls.[16] The relatively low incidence of death in the present study is likely related to the exclusion of patients with active lupus nephritis or central nervous system disease,[4] but the steroid-sparing effect and/or lower rate of organ damage accrual associated with belimumab might also contribute.[13, 14, 17]

In line with previous studies, there was an increase in the percentage of patients with low IgG;[14] however, the incidence of infections remained stable.

Sporadic cases of PML have rarely been reported in patients with SLE,[18] and rarely in those receiving belimumab.[19] In this study, there were no reported cases of PML; however, the study was not powered to assess PML incidence. Although it is likely that all immunosuppressants increase the risk of PML in patients with SLE,[20] this seems to remain a rare event and there is currently no evidence to suggest that belimumab further increases the risk.

As patient withdrawals occurred over time, there was an increase in the percentage of patients who achieved an SRI response. Although it is unlikely that patients with active disease might respond better to belimumab after a year or more of not responding to treatment, another way to examine disease rates is to consider the risk of flare in patients who may have already responded. The rates of all SFI flares and severe flares were highest in the first year of the study; from

Year 5, the rates were consistently low, indicating that patients who benefit from belimumab can maintain stable disease. Throughout the study, those patients remaining had reduced requirements for corticosteroids, and the percentage achieving low disease activity increased. Furthermore, patients continued to have serological improvements. These findings support the likelihood of sustained, long-term efficacy of belimumab in patients who respond.

During the 24-week follow-up period after study discontinuation, disease activity remained stable with little change in the percentages of the population who achieved an SRI response, experienced SFI flares, or had changes in prednisone dose. Longer-term studies with controls are required to fully investigate the effects of discontinuing belimumab because many factors may affect this, including duration of belimumab exposure, disease severity at discontinuation, possible selection bias in those who returned for follow up visits, and changes in SoC.

This study had several limitations. Because it was an open-label study with no placebo-controlled arm, and varied SoC, no treatment comparison can be made. Therefore, the results cannot be unequivocally attributed to belimumab.

In the double-blind phase of the study, some patients initially received lower doses of belimumab before switching to the licensed 10-mg/kg dose. In this analysis, the doses were pooled, given that there were no significant differences observed in the AE profile between the three doses in Phase II.[4] Patients had 1 year of acceptable response to placebo or belimumab plus SoC before beginning open-label treatment with belimumab; this resulted in patients' having more stable disease entering this continuation study. Baseline for all patients was the assessment prior to the first dose of belimumab; therefore, the first year reported for this study was double-blind exposure for patients randomized to belimumab and open-label exposure for patients randomized to placebo. Not surprisingly, patients who received placebo in the double-blind phase and still qualified as stable enough to continue had lower baseline disease activity compared with patients who received belimumab throughout (data not shown).

Patients who remained in the study were likely to be those who responded better or tolerated belimumab better than patients who withdrew; hence, the findings may not be representative of all patients with SLE. However, the population who entered the continuation study had similar baseline demographics to the double-blind study population.[4, 9] For the large percentage of patients who remained in the study (70.1% at 5 years, 60.1% at 7 years, and 44.3% at 10 years), the results suggest that patients who initially respond to belimumab and continue to receive treatment are likely to experience long-term benefits with continued or improved disease control.

In conclusion, this study describes the long-term safety and efficacy of belimumab in patients with SLE. It is the longest study of belimumab to date, with a high percentage of patients receiving treatment for over 10 years. This study provides further safety and efficacy data consistent with the Phase III long-term extension studies. It will be important to investigate the effects of stopping belimumab in patients who have achieved stable, long-term low-level disease activity; and a study (NCT02119156) is under way to investigate this question.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Wallace had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design: Wallace, Ginzler, Merrill, Furie, Stohl, and Petri.

Acquisition of data: Wallace, Ginzler, Merrill, Furie, Stohl, Chatham, Weinstein, McKay, McCune, and Petri.

Analysis and interpretation of data: Fettiplace, Roth, Ji, and Heath.

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Figure 1. A. Patient disposition; B. Withdrawals per study year (percentages calculated using number of patients starting study year as denominator)

mITT = modified intent-to-treat; N in Figure B = number of patients entering study year

Figure 2. Biomarkers. A. Percent of patients with immunoglobulin levels below the LLN, by study year (for patients with more than one value reported within a year, the last response within the year is summarized); B. Percent change from baseline in anti-dsDNA autoantibody levels among patients who were positive at baseline; C. Percent change from baseline in complement 3 levels among patients who had low complement 3 (<90 mg/dL) at baseline; D. Percent change from baseline in complement 4 levels among patients who had low complement 4 (<16 mg/dL) at baseline

dsDNA = double-stranded DNA; Ig = immunoglobulin; LLN = lower limit of normal; W = week; Y = Year

Figure 3 A. SRI4 response; B. SELENA-SLEDAI; C. Percent of patients with no new BILAG A organ domain score and no more than 1 new BILAG B organ domain score from baseline; D. PGA score

BILAG = British Isles Lupus Assessment Group; PGA = Physician's Global Assessment; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus-National Assessment-SLE Disease Activity Index; SLE = systemic lupus erythematosus; SRI = Systemic Lupus Erythematosus Responder Index; W = Week; Y = Year. N numbers displayed under Figures A, B and D correspond with the final time point of each year.

Figure 4. A. Rates of all and severe SFI flares; B. Median percent change in prednisone dose from baseline; C. Percent of patients with a prednisone dose increase from ≤7.5 mg/day or a reduction from >7.5 mg/day; D. Percent of patients with low disease activity (defined as SELENA-SLEDAI ≤2 and prednisone dose ≤5 mg/day).

pt-y = patient-years; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus National Assessment-SLE Disease Activity Index; SFI = SELENA-SLEDAI Flare Index; SLE = systemic lupus erythematosus; W = Week; Y = Year.

Table 1. Baseline (prior to the first dose of belimumab) patient demographics and clinical characteristics

Characteristic	Study population (N=296)
Female, n (%)	276 (93.2)
Mean age, years ± SD	43.0 ± 11.58
Ethnicity, n (%)	
Hispanic or Latino	54 (18.2)
Not Hispanic or Latino	242 (81.8)
Race, n (%)	
White	215 (72.6)
Black or African American	68 (23.0)
Other	13 (4.4)
Mean disease duration, years ± SD	9.1 ± 7.80
Mean SELENA-SLEDAI ± SD,	8.4 (4.68)
SELENA-SLEDAI ≤9, n (%)	190 (64.2)
SELENA-SLEDAI ≥10, n (%)	106 (35.8)
At least 1A or 2B BILAG scores, n (%)	168 (56.8)
Mean PGA score ± SD)	1.30 ± 0.571
At least 1 SFI flare,* n (%)	47 (15.9)
At least 1 severe SFI flare,* n (%)	9 (3.0)
Corticosteroids (prednisone equivalent dose), n (%)	
None	105 (35.5)
≤7.5 mg/day	99 (33.4)
>7.5 mg/day	92 (31.1)
Low C3 (<90 mg/dL) and/or low C4 (<16 mg/dL),† n (%)	135 (46.1)
Anti-dsDNA positive (≥30 IU/mL), n (%)	149 (50.3)

ANA titer,‡ n (%)	
≥80	208 (81.3)
<80	48 (18.8)

*For patients who received belimumab in the double-blind phase, any time prior to study entry; for patients who received placebo in the double-blind phase, between the last visit in the double-blind phase and first dose of belimumab in the open-label phase; †data available for 293 patients; ‡data available for 256 patients.
ANA = antinuclear antibody; BILAG = British Isles Lupus Assessment Group; C = complement; dsDNA = double-stranded DNA; PGA = Physician's Global Assessment; SD = standard deviation; SELENA-SLEDAI = Safety of Estrogens in Lupus Erythematosus-National Assessment-SLE Disease Activity Index; SFI = SELENA-SLEDAI Flare Index; SLE = systemic lupus erythematosus

Table 2. Summary of the number and rate of AEs (overall and by study year)

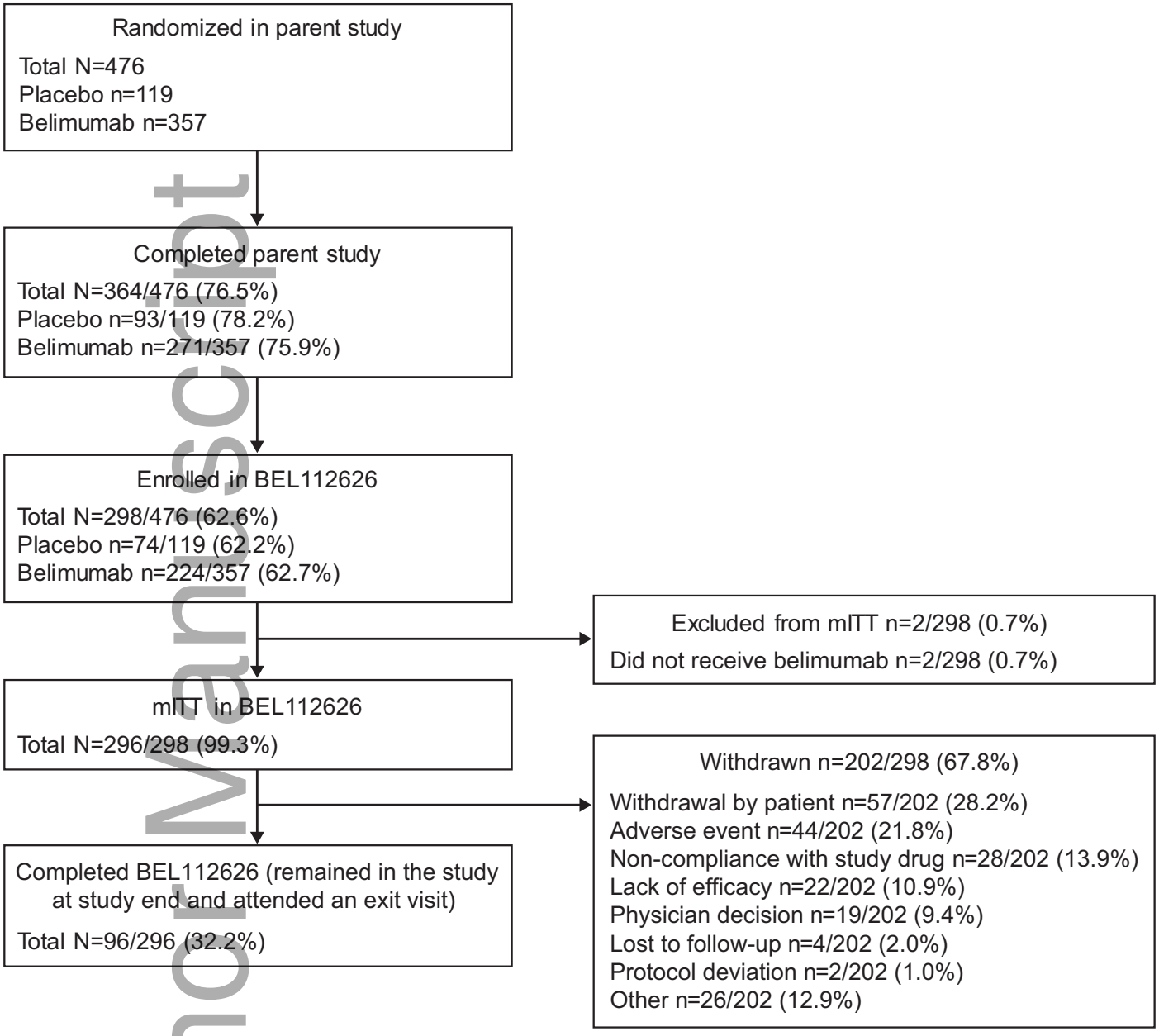
Number of events (rate/100 pt-yrs)	Study year, pt-yrs						
	Overall	**1**	**2**	**3**	**4**	**5**	**6**
	2416 pt-yrs	**295 pt-yrs**	**289 pt-yrs**	**260 pt-yrs**	**236 pt-yrs**	**218 pt-yrs**	**199 pt-yrs**
AEs	18,259 (755.8)	3554 (1203.1)	2796 (967.9)	2083 (801.7)	1639 (694.6)	1424 (653.3)	1319 (661.6)
AEs resulting in treatment discontinuation	44 (1.8)	2 (0.7)	3 (1.0)	3 (1.2)	7 (3.0)	5 (2.3)	6 (3.0)
At least 1 serious AE	719 (29.8)	55 (18.6)	65 (22.5)	91 (35.0)	47 (19.9)	93 (42.7)	65 (32.6)
Serious infections/infestations	134 (5.5)	11 (3.7)	15 (5.2)	13 (5.0)	10 (4.2)	9 (4.1)	8 (4.0)
Infections of special interest[†]	124 (5.1)	13 (4.4)	19 (6.6)	9 (3.5)	13 (5.5)	12 (5.5)	12 (6.0)
All malignant neoplasms (except non-melanoma skin cancer)	14 (0.6)	0	0	1 (0.4)	1 (0.4)	4 (1.8)	1 (0.5)
Depression	237 (9.8)	51 (17.3)	36 (12.5)	17 (6.5)	32 (13.6)	18 (8.3)	11 (5.5)
Suicide/self-injury	6 (0.2)	1 (0.3)	1 (0.3)	1 (0.4)	0	2 (0.9)	1 (0.5)
Death[‡]	8 (0.3)	1 (0.3)	0	1 (0.4)	1 (0.4)	0	1 (0.5)
	7	**8**	**9**	**10**	**11**	**11+***	
	185 pt-yrs	**171 pt-yrs**	**160 pt-yrs**	**152 pt-yrs**	**104 pt-yrs**	**36 pt-yrs**	
AEs	1357 (733.3)	1228 (717.4)	1047 (656.0)	861 (612.8)	629 (603.4)	154 (426.7)	

AEs resulting in treatment discontinuation	6 (3.2)	1 (0.6)	3 (1.9)	5 (3.6)	2 (1.9)	0
At least 1 serious AE	66 (35.7)	63 (36.8)	46 (28.8)	47 (33.5)	27 (25.9)	19 (52.6)
Serious infections/infestations	16 (8.6)	12 (7.0)	8 (5.0)	6 (4.3)	7 (6.7)	5 (13.9)
Infections of special interest[†]	10 (5.4)	10 (5.8)	4 (2.5)	9 (6.4)	5 (4.8)	3 (8.3)
All malignant neoplasms (except non-melanoma skin cancer)	1 (0.5)	0	2 (1.3)	3 (2.1)	0	0
Depression	23 (12.4)	19 (11.1)	11 (6.9)	9 (6.4)	3 (2.9)	0
Suicide/self-injury	0	0	0	0	0	0
Death[‡]	2 (1.1)	0	0	1 (0.7)	0	0

*Includes AEs that occurred from Year 11 to the end of the study (Year 13) and the follow-up period; [†]included opportunistic infections, tuberculosis, herpes zoster (recurrent and disseminated) and sepsis; [‡]causes of death: Year 1, coronary artery disease; Year 3, suicide; Year 4, pneumonia; Year 6, cardiac arrest; Year 7, acute respiratory distress syndrome, respiratory failure; Year 10, retroperitoneal hemorrhage; one death (pneumonia) occurred during the follow-up phase.

AE = adverse event; pt-yrs, patient-years.

A.



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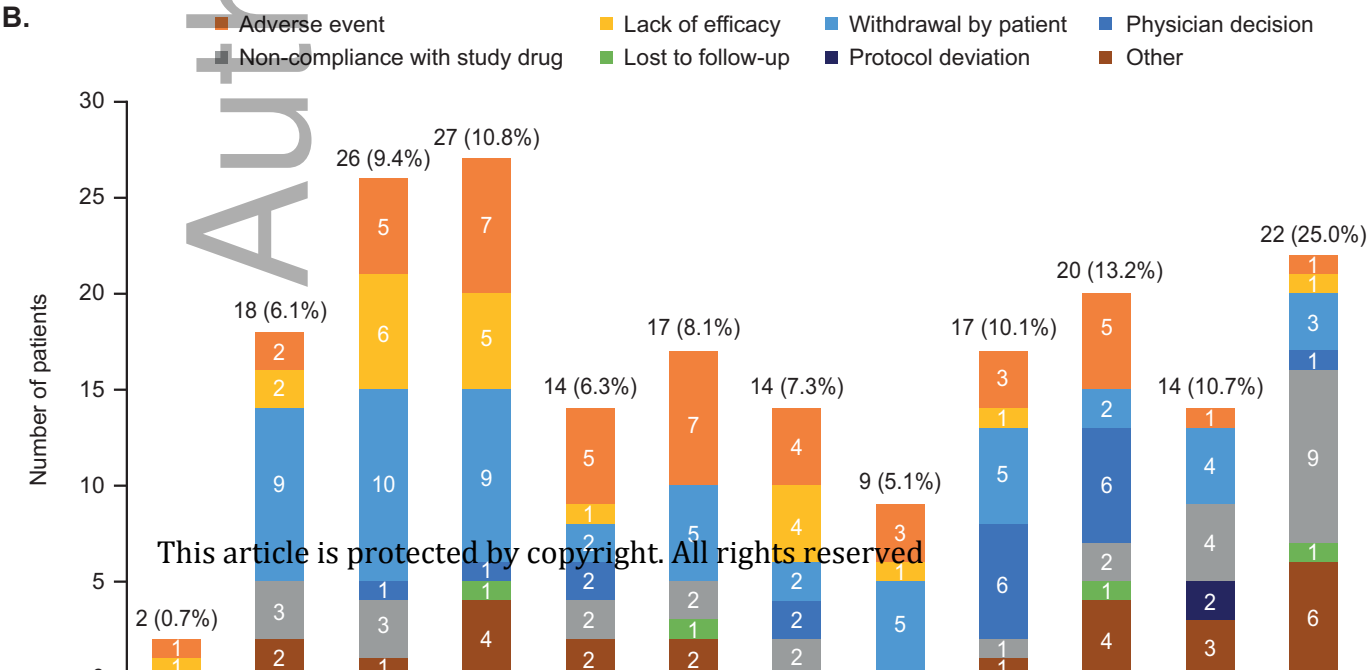

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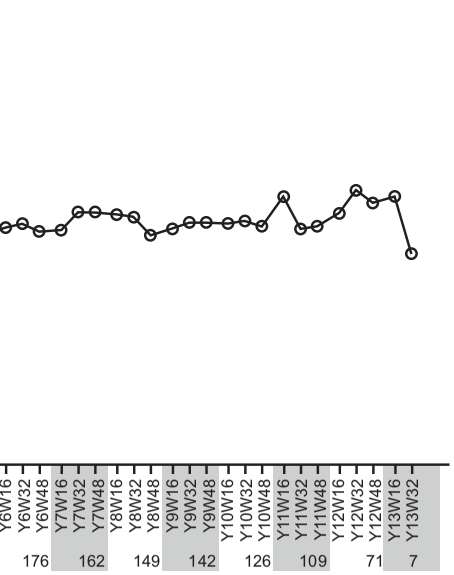

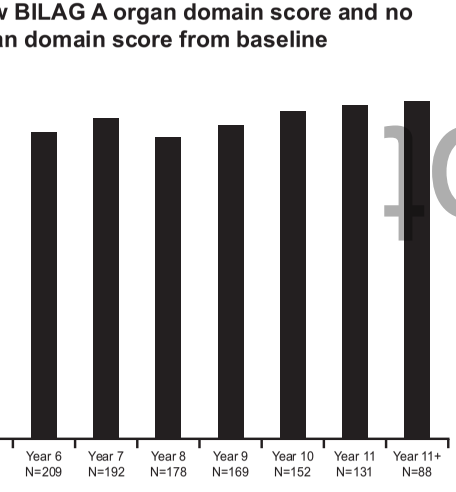

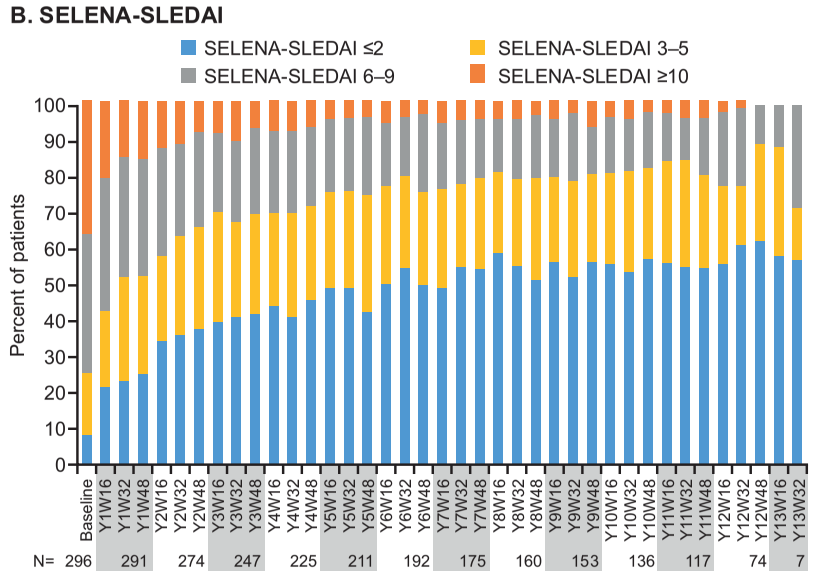

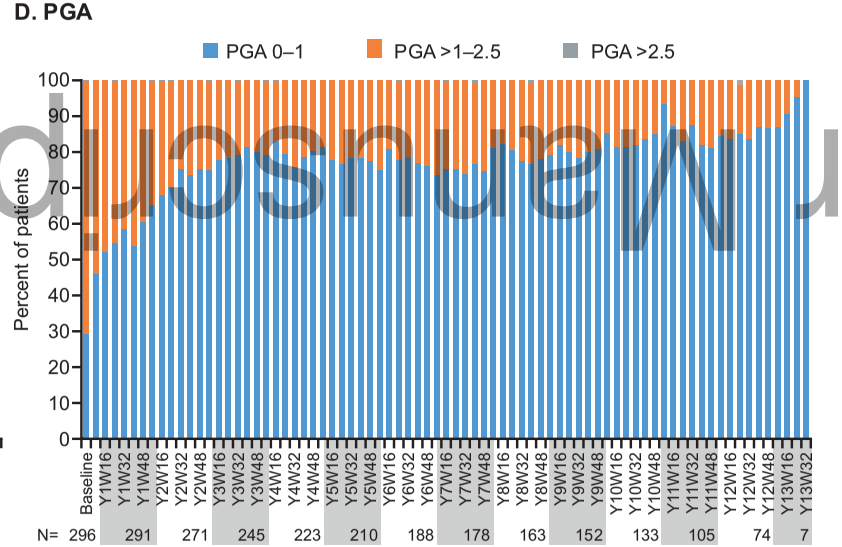

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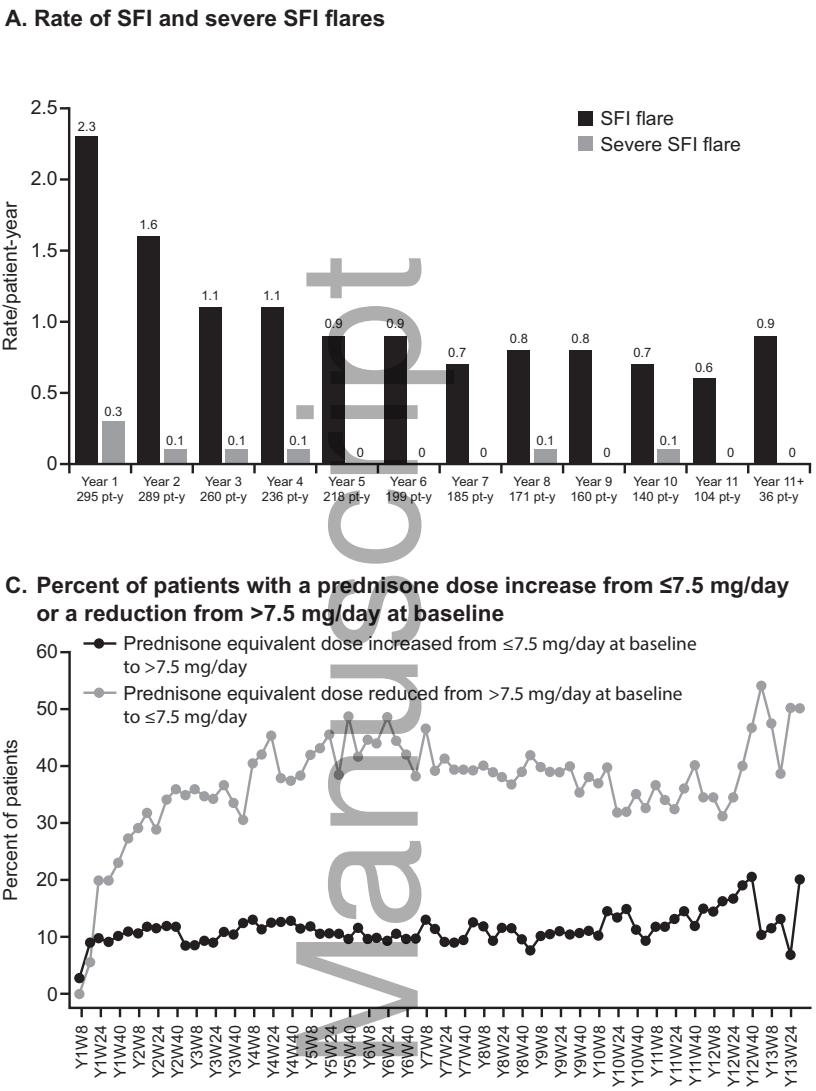

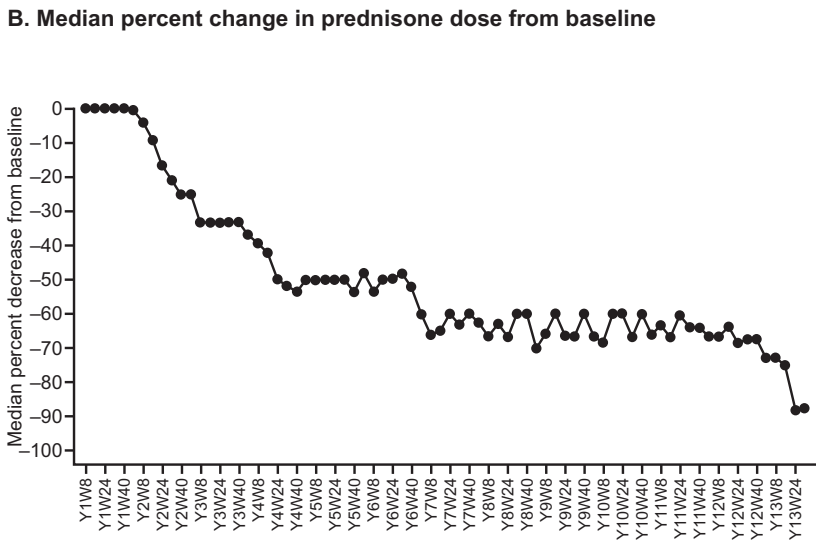

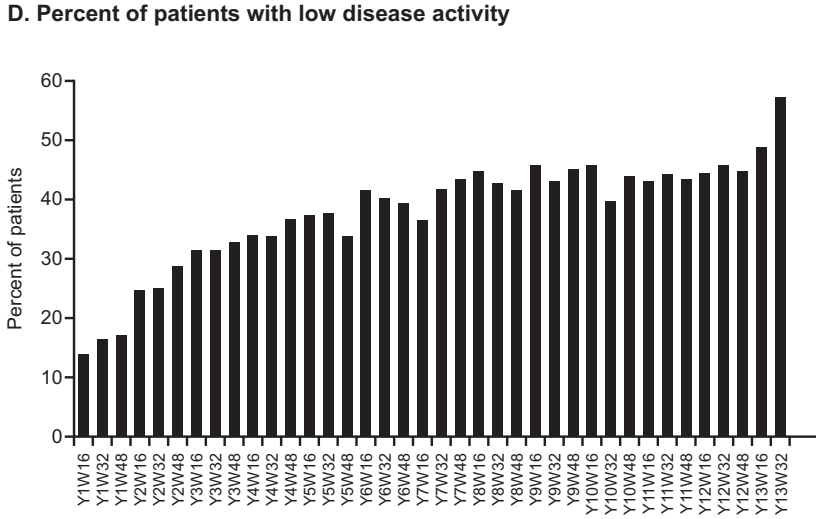

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